Complete Summary

GUIDELINE TITLE

The pharmacology and management of the vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.

BIBLIOGRAPHIC SOURCE(S)

Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):204S-33S. [329 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On December 1, 2005, Novo Nordisk and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of revisions to the WARNINGS and ADVERSE REACTIONS sections of the prescribing information for NovoSeven, to provide updated safety information on thrombotic and thromboembolic adverse events, based on clinical studies in non-hemophilia patients and on post-marketing safety surveillance. A clinical study in elderly, non-hemophiliac, intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of NovoSeven, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Thromboembolic disorders including the following:

- Primary and secondary venous thromboembolism
- Systemic embolism in patients with prosthetic heart valves or atrial fibrillation
- Acute myocardial infarction in high-risk men
- Stroke, recurrent infarction, or death in patients with acute myocardial infarction
- Systemic embolism in high-risk patients with mitral stenosis

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To describe the antithrombotics effects of vitamin K antagonists (VKAs)
- To provide evidence-based recommendations concerning the monitoring of anticoagulation intensity, the clinical applications of VKA therapy, and the optimal therapeutic range of VKAs

TARGET POPULATION

Patients requiring oral anticoagulant therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Pharmacotherapy

1. Vitamin K antagonists (VKAs)*
2. Low-molecular-weight heparin (LMWH)
3. Unfractionated heparin (UFH)
4. Reversal of VKAs:
    - Vitamin K1
    - Fresh plasma
    - Prothrombin complex concentrate
    - Recombinant factor VIIa
5. Tranexamic acid mouthwash
6. Epsilon amino caproic acid mouthwash

*Note: Since warfarin is the most commonly used VKA worldwide, warfarin was used interchangeably with VKA or coumarin.

Monitoring

1. Prothrombin time (PT)
2. International normalized ratio (INR)

MAJOR OUTCOMES CONSIDERED

- Incidence of thrombosis
- Recurrent thromboembolism
- Incidence of major and minor hemorrhage
- Time to achieve therapeutic international normalized ratio (INR)
- Anticoagulant response
- Maintenance dose
- Time in the therapeutic range (TTR)
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. Prior to searching for the evidence, methodological experts and librarians reviewed each question to ensure that the librarians could derive a comprehensive search strategy.

In specifying eligibility criteria, authors not only identified patients, interventions, and outcomes, but also methodological criteria. For most therapeutic studies, authors restricted eligibility to randomized controlled trials (RCTs).

For many questions, RCTs did not provide sufficient data, and article authors also included observational studies. This was also true when randomized trials were not the most appropriate design to use for addressing the research question. In particular, randomized trials are not necessarily the best design to understand risk groups (e.g., the baseline or expected risk of a given event for certain subpopulations). Because there are no interventions examined in questions about prognosis, one replaces interventions by the exposure, which is time.

Identifying the Evidence

To identify the relevant evidence, a team of librarians at the University at Buffalo conducted comprehensive literature searches. For each question the authors provided, the librarians developed sensitive (but not specific) search strategies, including all languages, and conducted separate searches for systematic reviews, RCTs, and, if applicable, observational studies. The librarians searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and Cochrane Register of Controlled Trial, the ACP Journal Club, MEDLINE, and Embase for studies published between 1966 and June 2002 in any language. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration (full strategy available in Appendix online at: http://www.chestjournal.org/content/vol126/3_suppl_1).

For observational studies, they restricted their searches to human studies. Searches were not further restricted in terms of methodology. While increasing the probability of identifying all published studies, this sensitive approach resulted in large number of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search and removed any apparently irrelevant citations. These irrelevant citations included press news, editorials, narrative reviews, single case reports, animal studies (any nonhuman studies), and letters to the editor. Authors included data from abstracts of recent meetings if reporting was transparent and all necessary data for the formulation of a recommendation were available. The guideline developers did not explicitly use Internet sources to search for research data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) (and the methodological quality of the underlying evidence (A, B, C+, or C). See "Rating Scheme for the Strength of the Recommendations."

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Summarizing Evidence

The electronic searches also included searching for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation.

Pooled analyses from high-quality systematic reviews formed, wherever possible, the evidence base of the recommendations. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for a greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefit and downsides (i.e., risk, burden, and cost).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The strength of any recommendation depends on the following two factors: the trade-off between the benefits and the risks, burdens, and costs; and the strength of the methodology that leads to the treatment effect. The guideline developers grade the trade-off between benefits and risks in the two categories: 1, in which the trade-off is clear enough that most patients, despite differences in values, would make the same choice; and 2, in which the trade-off is less clear, and individual patients' values will likely lead to different choices.

When randomized trials provide precise estimates suggesting large treatment effects, and the risks and costs of therapy are small, treatment for average patients with compatible values and preferences can be confidently recommended.

If the balance between benefits and risks is in doubt, methodologically rigorous studies providing Grade A evidence and recommendations may still be weak (Grade 2). Uncertainty may come from less precise estimates of benefit, harm, or costs, or from small effect sizes.

There is an independent impact of validity and consistency, and the balance of positive and negative impacts of treatment on the strength of recommendations.

In situations in which there is doubt about the value of the trade-off, any recommendation will be weaker, moving from Grade 1 to Grade 2.

Grade 1 recommendations can only be made when there is a relatively clear picture of both the benefits and the risks, burdens, and costs, and when the balance between the two clearly favors recommending or not recommending the intervention for the typical patient with compatible values and preferences. A number of factors can reduce the strength of a recommendation, moving it from Grade 1 to Grade 2. Uncertainty about a recommendation to treat may be introduced if the following conditions apply: (1) the target event that is trying to be prevented is less important (confident recommendations are more likely to be made to prevent death or stroke than asymptomatic deep vein thrombosis); (2) the magnitude of risk reduction in the overall group is small; (3) the probability of the target event is low in a particular subgroup of patients; (4) the estimate of the treatment effect is imprecise, as reflected in a wide confidence interval (CI) around the effect; (5) there is substantial potential harm associated with therapy; or (6) there is an expectation for a wide divergence in values even among average or typical patients. Higher costs would also lead to weaker recommendations to treat.

The more balanced the trade-off between benefits and risks, the greater the influence of individual patient values in decision making. Virtually all patients, if they understand the benefits and risks, will take aspirin after experiencing a myocardial infarction (MI) or will comply with prophylaxis to reduce the risk of thromboembolism after undergoing hip replacement. Thus, one way of thinking about a Grade 1 recommendation is that variability in patient values is unlikely to influence treatment choice in average or typical patients.

When the trade-off between benefits and risks is less clear, individual patient values may influence treatment decisions even among patients with average or typical preferences.

Grade 2 recommendations are those in which variation in patient values or individual physician values will often mandate different treatment choices, even among average or typical patients. An alternative, but similar, interpretation is that a Grade 2 recommendation suggests that clinicians conduct detailed conversations with patients to ensure that their ultimate recommendation is consistent with the patient's values.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	Randomized controlled trials (RCTs) without important	Strong recommendation; can apply to most patients in most

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		limitations	circumstances without reservation
1C+	Clear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws*)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from	Weak recommendation; best action may differ depending on circumstances or patients' or societal values

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
		observational studies	
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws*)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

*These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.

COST ANALYSIS

While conference participants agreed that recommendations should reflect economic considerations, incorporating costs is fraught with difficult challenges. For most recommendations, formal economic analyses are unavailable. Even when analyses are available, they may be methodologically weak or biased. Furthermore, costs differ radically across jurisdictions, and even sometimes across hospitals within jurisdictions.

Because of these challenges, the guideline developers consider economic factors only when the costs of one therapeutic option over another are substantially different within major jurisdictions in which clinicians make use of their recommendations. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far better than some of the interventions that are designated as Grade 1A. This will likely be true for all less industrialized countries and, with the increasing promotion of expensive drugs with marginal benefits, may be increasingly true for wealthier nations. Furthermore, recommendations change (either in direction or with respect to grade) only when the guideline developers believe that costs are high in relation to benefits. Instances in which costs have influenced recommendations are labeled in the "values and preferences" statements associated with the recommendation.

Cost-Effectiveness of Usual Care (UC) vs. Anticoagulation Management Service (AMS)

Because of improved outcomes with fewer hospitalizations and emergency department visits, the management of anticoagulation by an AMS may prove to be more cost-effective, as demonstrated by a number of investigators suggesting a "cost avoidance" of approximately $1,000 per patient year of therapy. These observations need to be validated by randomized studies.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline authors formulated draft recommendations prior to the conference that served as the foundation for authors to work together and critique the recommendations. Drafts of all articles including draft recommendations were available for review during the conference. A representative of each article presented potentially controversial issues in their recommendations at plenary meetings. Article authors met to integrate feedback, to consider related recommendations in other articles, and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who had provided critical feedback. Finally, the editors of this supplement harmonized the articles and resolved remaining disagreements through facilitated discussion.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The rating scheme is defined at the end of the "Major Recommendations" field.

Please refer to the original full-length guideline document for a detailed description of the pharmacology and monitoring of vitamin K antagonists (VKAs), the pharmacokinetics and pharmacodynamics of warfarin (including genetic and environmental factors), the antithrombotics effect of VKAs, monitoring anticoagulation intensity, and clinical applications of VKA therapy.

The Appropriate Dose for Initiation of Oral Coagulants

1. The guideline developers suggest the initiation of oral anticoagulation with doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response (Grade 2B).

Anticoagulation in the Elderly

1. In the elderly, for patients who are debilitated, malnourished, have congestive heart failure, or have liver disease, the guideline developers suggest the use of a starting dose of ≤5 mg (Grade 2C).

Frequency of Monitoring Oral Anticoagulation Therapy

1. The guideline developers suggest starting INR monitoring after the initial two or three doses of oral anticoagulation therapy (Grade 2C).
2. For patients who are receiving a stable dose of oral anticoagulants, the guideline developers suggest monitoring at an interval of no longer than every 4 weeks (Grade 2C).

Management of Dosing When the INR is Nontherapeutic

1. For patients with INRs above the therapeutic range, but <5.0 who have no significant bleeding, lower the dose or omit the dose, monitor more frequently, and resume therapy at a lower dose when the INR is in the therapeutic range. If only minimally above the therapeutic range, no dose reduction may be required (all Grade 2C).
2. For patients with INRs of ≥5.0 but <9.0 who have no significant bleeding, omit the next one or two doses, monitor more frequently, and resume therapy at a lower dose when the INR is in the therapeutic range. Alternatively, omit a dose and administer vitamin K1 (1 to 2.5 mg orally), particularly if the patient is at an increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (≤5 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 hours. If the INR is still high, additional vitamin K1 (1 to 2 mg orally) can be given (all Grade 2C).
3. For patients with INRs of ≥9.0 and no significant bleeding, hold warfarin therapy and administer a higher dose of vitamin K1 (5 to 10 mg orally) with the expectation that the INR will be reduced substantially in 24 to 48 hours. Monitor the patient more frequently and use additional vitamin K1 if necessary. Resume therapy at a lower dose when INR is in the therapeutic range (all Grade 2C).
4. In patients with serious bleeding and elevated INRs, the guideline developers recommend holding warfarin therapy and administering vitamin K1 (10 mg by slow intravenous [IV] infusion) supplemented with fresh plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. Vitamin K1 administration can be repeated every 12 hours (all Grade 1C).
5. In patients with life-threatening bleeding and elevated INRs, the guideline developers recommend holding warfarin therapy and administering prothrombin complex concentrate or recombinant factor VIIa supplemented with vitamin K1 (10 mg by slow IV infusion). Repeat the procedure if necessary, depending on the INR (Grade 1C).
6. In patients with mild to moderately elevated INRs who have no major bleeding, the guideline developers suggest that vitamin K be administered orally rather than subcutaneously (SC) (Grade 1A).

Management of Dosing When an Invasive Procedure is Required

1. For patients with a low risk of thromboembolism, stop warfarin therapy approximately 4 days before they undergo surgery, allow the INR to return to near-normal values, briefly use postoperative prophylaxis (if the intervention increases the risk of thrombosis) with a low dose of unfractionated heparin (UFH) (5,000 U SC) or a prophylactic dose of low-molecular-weight heparin (LMWH), and simultaneously begin warfarin therapy. Alternatively, a low dose of UFH or a prophylactic dose of LMWH also can be used preoperatively (all Grade 2C).
2. For patients with an intermediate risk of thromboembolism, stop warfarin approximately 4 days before surgery, allow the INR to fall, cover the patient beginning 2 days preoperatively with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH, and then commence administration of a low dose of UFH (or LMWH) and warfarin postoperatively. (Grade 2C).
3. For patients with a high risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery to allow the INR to return to normal at the time of surgery, and begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 days preoperatively). UFH can be administered as an SC injection on an outpatient basis and as a continuous IV infusion after hospital admission in preparation for surgery and should be discontinued approximately 5 hours before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. An alternative is to continue to use SC UFH or LMWH preoperatively and to stop therapy 12 to 24 h before surgery with the expectation that the anticoagulant effect will be very low or have worn off at the time of surgery, then commence administering a low dose of UFH (or LMWH) and warfarin postoperatively (Grade 2C).
4. For patients with a low risk of bleeding, continue warfarin therapy at a lower dose and operate at an INR of 1.3 to 1.5. The dose of warfarin can be lowered 4 or 5 days before surgery. Warfarin therapy then can be restarted postoperatively, supplemented with a low dose of UFH (5,000 U SC) or a prophylactic dose of LMWH, if necessary (Grade 2C).
5. In patients who are undergoing dental procedures with a need to control local bleeding, the guideline developers suggest the use of tranexamic acid mouthwash (Grade 2B) or epsilon amino caproic acid mouthwash without interrupting anticoagulant therapy (Grade 2B).

Therapeutic Range in the Presence of a Lupus Inhibitor

1. In patients who have a lupus inhibitor and who have no additional risk factors and have not failed to respond to therapy, the guideline developers suggest a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) (Grade 2B). In patients who have recurrent thromboembolic events with a therapeutic INR or other additional risk factors for thromboembolic events, the guideline developers suggest a target INR of 3.0 (INR range, 2.5 to 3.5) (Grade 2C).

Models of Anticoagulation Monitoring and Management

1. The guideline developers recommend that physicians who manage oral anticoagulation therapy do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions (Grade 1C+).

Definitions

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
1A	Clear	Randomized controlled trials (RCTs) without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws*)	Strong recommendation; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values

Grade of Recommendation	Clarity of Risk/Benefit	Methodological Strength of Supporting Evidence	Implications
2C+	Unclear	No RCTs, but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	RCTs with important limitations (inconsistent results, methodological flaws*)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

*These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate monitoring and management of patients who require treatment with vitamin K antagonists (VKAs)

POTENTIAL HARMS

- Refer to Table 2 of the original guideline document entitled "Drug and Food Interactions with Warfarin by Level of Supporting Evidence and Direction of Interaction" for information on potentiation, inhibition, and no effect interactions.
- Refer to Table 3 of the original guideline document entitled "Enzyme-inducing Drug Interactions with Warfarin" for information on inducing agents, isoenzyme induced, expected onset, anticipated dosage adjustments, and expected offset.
- Refer to Table 4 of the original guideline document entitled "Potential Problems with International Normalized Ratio (INR) (Causes of Erroneous INR)" for information on problems with INR monitoring.
- Bleeding, the most feared and major complication of oral anticoagulant therapy, is closely related to the intensity of anticoagulation.
- High doses of vitamin K1, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for a week or more.
- Intravenous (IV) injection of vitamin K1 may be associated with anaphylactic reactions, although such reactions have even been described with non-IV routes of administration.
- Other than hemorrhage, the most important side effect of warfarin is skin necrosis. This uncommon complication is usually observed on the third to eighth day of therapy, and is caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat.
- A variant of this syndrome also attributed to a severe, warfarin-induced, depletion of protein C is the occurrence of venous limb gangrene during warfarin treatment of cancer-associated deep vein thrombosis.
- Refer to Tables 8, 9, and 10 of the original guideline document for information on the frequency of major hemorrhage/thromboembolism in patients managed under an anticoagulation management service (AMS), the frequency of major hemorrhage/thromboembolism in patients managed under usual care vs. AMS, and the frequency of major hemorrhage/thromboembolism in patients managed under usual care, respectively.

Subgroups Most Likely to Experience Harms

Several patient characteristics have been shown to be associated with higher odds of bleeding during anticoagulation therapy. The patient factor that most consistently has been demonstrated to be predictive of major bleeding is a history of bleeding (especially gastrointestinal [GI] bleeding). Other factors that have been shown to be associated include a history of stroke and the presence of a serious comorbid condition such as renal insufficiency, anemia, or hypertension.

CONTRAINDICATIONS

CONTRAINDICATIONS

The management of patients with warfarin-induced skin necrosis who require lifelong anticoagulant therapy is problematic. Therapy with warfarin is considered to be contraindicated, and long-term heparin therapy is inconvenient and is associated with osteoporosis.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Interpreting the Recommendations

Clinicians, third-party payers, institutional review committees, or the courts should not construe these guidelines in any way as absolute dictates. In general, anything other than a Grade 1A recommendation indicates that the article authors acknowledge that other interpretations of the evidence, and other clinical policies, may be reasonable and appropriate. Even Grade 1A recommendations will not apply to all circumstances and all patients. For instance, the guideline developers have been conservative in their considerations of cost and have seldom downgraded recommendations from Grade 1 to Grade 2 on the basis of expense. As a result, in jurisdictions in which resource constraints are severe, alternative allocations may serve the health of the public far better than some of the interventions that are designated as Grade 1A. This will likely be true for all less industrialized countries and, with the increasing promotion of expensive drugs with marginal benefits, may be increasingly true for wealthier nations.

Similarly, following Grade 1A recommendations will at times not serve the best interests of patients with atypical values or preferences or of those whose risks differ markedly from those of the usual patient. For instance, consider patients who find anticoagulant therapy extremely aversive, either because it interferes with their lifestyle (e.g., prevents participation in contact sports) or because of the need for monitoring. Clinicians may reasonably conclude that following some Grade 1A recommendations for anticoagulation therapy for either group of patients will be a mistake. The same may be true for patients with particular comorbidities (e.g., a recent gastrointestinal bleed or a balance disorder with repeated falls) or other special circumstances (e.g., very advanced age) that put them at unusual risk.

The guideline developers trust that these observations convey their acknowledgment that no recommendations or clinical practice guidelines can take into account the often compelling and unique features of individual clinical circumstances. No clinician, and no body charged with evaluating a clinician's actions, should attempt to apply these recommendations in a rote or blanket fashion.

Limitations of Guideline Development Methods

The limitations of these guidelines include the possibility that some authors followed this methodology more closely than others, although the development process was centralized and supervised by the editors. Second, it is possible that the guideline developers missed relevant studies despite the comprehensive searching process. Third, the guideline developers did not centralize the

methodological evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines. Fourth, if high-quality meta-analyses were unavailable, the guideline developers did not statistically pool primary study results using meta-analysis. Finally, sparse data on patient preferences and values, resources, and other costs represent additional limitations that are inherent to most guideline development methods.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Guideline Implementation Strategies

A full review of implementation strategies for practice guidelines is provided in the companion document entitled "Antithrombotic and Antithrombolytic Therapy: From Evidence to Application." The review suggests that there are few implementation strategies that are of unequivocal, consistent benefit, and that are clearly and consistently worth resource investment. The following is a summary of the recommendations (see "Major Recommendations" for a definition of the recommendation grades).

To encourage uptake of guidelines, the guideline developers recommend that appreciable resources be devoted to distribution of educational material (Grade 2B).

They also suggest that:

- Few resources be devoted to educational meetings (Grade 2B)
- Few resources be devoted to educational outreach visits (Grade 2A)
- Appreciable resources be devoted to computer reminders (Grade 2A)
- Appreciable resources be devoted to patient-mediated interventions to encourage uptake of the guidelines (Grade 2B)
- Few resources be devoted to audit and feedback (Grade 2B)

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Resources
Slide Presentation
Tool Kits

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):204S-33S. [329 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Sep

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

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GUIDELINE COMMITTEE

American College of Chest Physicians Consensus Panel on Antithrombotic and Thrombolytic Therapy

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Jack Ansell, MD; Jack Hirsh, MD, FCCP; Leon Poller, MD; Henry Bussey, PharmD, FCCP; Alan Jacobson, MD; Elaine Hylek, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Ansell has received research funding from AstraZeneca, Aventis, Sanofi-Synthelabo-Organon, Bristol-Myers Squibb. Dr. Ansell has received honoraria for his participation on advisory boards and/or as a speaker at educational events from AstraZeneca, Aventis, Sanofi-Synthelabo-Organon, Wyeth Ayerst, Yamanouchi, Roche Diagnostics, HemoSense, International Technedyne.

Dr. Hirsh has received research funding from AstraZeneca and has received honararia for his participation on advisory boards and/or as a speaker at educational events from AstraZeneca.

Dr. Poller is employed in an honorary capacity as Professor in the University of Manchester. He receives research funding only from the European Community and Manchester Thrombosis Research Foundation, a registered charity. No honoraria have been received from industry for the past 3 years.

Dr. Bussey has received research funding from Aventis, Organon-Sanofi-Synthelabo, AstraZeneca, Bristol-Myers Squibb, Bertek Pharmaceuticals, and Novartis and has participated on advisory boards and/or research steering committees for Aventis, Organon-Sanofi-Synthelabo, and AstraZeneca. He also has received speaking honoraria from and/or served as a consultant for Aventis, AstraZeneca, Bristol-Myers Squibb, and Organon-Sanofi-Synthelabo.

Dr. Jacobson has received research funding from AstraZeneca, Bristol-Myers Squibb, Aventis, Sanofi, Organon, Roche Diagnostics, Hemosense, International Technidyne, and Lifescan, and has received honoraria for his participation on advisory boards and/or as a speaker at educational events from AstraZeneca, Aventis, Bristol-Myers Squibb, and Lifescan.

Dr. Hylek has received research funding from Pfizer and Bristol-Myers Squibb and has received honoraria for participation as a speaker at an educational event from Bristol-Myers Squibb.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Evidence-based guidelines. Northbrook, IL: ACCP, 2004 Sep.

- Methodology for guideline development for the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Applying the grades of recommendation for antithrombotic and thrombolytic therapy: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Hemorrhagic complications of anticoagulant treatment: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Antithrombotic and thrombolytic therapy: from evidence to application: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.
- Platelet-active drugs: the relationships among dose, effectiveness, and side effects: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Northbrook, IL: ACCP, 2004 Sep.

Electronic copies: Available from the Chest - The Cardiopulmonary and Critical Care Journal Web site.

Print copies: Available from the American College of Chest Physicians (ACCP), Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

The following is also available:

- Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-based guidelines; quick reference guide. Northbrook, IL: ACCP, 2004 Sep. Personal Digital Assistant (PDA) download available at ACCP Web site.

Additional implementation tools are also available:

- Clinical resource: antithrombotic and thrombolytic therapy. Northbrook, IL. ACCP, 2004. Ordering information: Available from the ACCP Web site.

PATIENT RESOURCES

The following is available:

- A patient's guide to antithrombotic and thrombolytic therapy. In: Clinical resource: antithrombotic and thrombolytic therapy. Northbrook (IL): American College of Chest Physicians (ACCP). 2004.

Ordering information is available from the ACCP Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the

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